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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/696,488	10/29/2003	Bernard Cuenoud	20890-US-CNT2	7737

75074 7590 07/09/2010

NOVARTIS INSTITUTES FOR BIOMEDICAL RESEARCH, INC.
220 MASSACHUSETTS AVENUE
CAMBRIDGE, MA 02139

EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
07/09/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

NIBR.MAILDATA@NOVARTIS.COM
PATRICIA.HOFSTETTER@NOVARTIS.COM

Office Action Summary	Application No.	Applicant(s)	
	10/696,488	CUENOUD ET AL.	
	Examiner	Art Unit	
	J. E. ANGELL	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 June 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Action is in response to the communication filed on 6/7/2010.

The amendment filed 6/7/2010 is acknowledged and has been entered.

Claims 1-58 are currently pending in the application and are addressed herein.

Upon further consideration of the claims and updating and reviewing the search and the prior art, the claims are not allowable in view of the rejections set forth herein. The rejections are not necessitated by amendment, therefore, this action is made non-final.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-58 are rejected under 35 U.S.C. 103(a) as being unpatentable over McGee et al. (WO 94/02501; cited by Applicants).

The instant claims read on oligonucleotide derivatives/compounds of formula (I), (Ia), (Ic) (including antisense oligonucleotides), methods for producing said oligonucleotide derivatives/compounds, and methods of modulating expression including therapeutic treatment comprising administration of a composition comprising said oligonucleotide derivatives/compounds. The oligonucleotide derivatives of the instant application comprise a genus compounds comprising 2'-O-alkyl-amino (o alkyl-N-substituted) modifications.

McGee et al. disclose an oligonucleotide derivative comprising a nucleoside building block of the formula (I) of the instant application, wherein R1, R2, and R3 are either H or an alkyl group, and B is a nucleic acid base (see pages 7-24, and claims 1-69). The oligonucleotide derivatives of McGee et al. comprise modifications at the 2'-O of the ribofuranosyl ring, wherein said modifications enhance the pharmacokinetic and pharmacodynamic properties of an oligonucleotide. McGee et al. also teaches that oligonucleotides comprising 2'-O modifications such as 2'-O-alkyl and 2'-O-allyl have enhanced nuclease stability (pages 4-5). The oligonucleotides of McGee et al. include modifications wherein the 2'-O group is substituted by X, wherein X = R1-(R2)n; R1 = C3-20 alkyl, C4-20 alkenyl, C2-20 alkynyl; R2 = halo, OH, SH, keto, CO2H, NO2, nitroso, cyano, CF3, CF3O, alkoxy, alkylthio, alkyl amino, NH2, phthalimido, imidazolyl, N3, hydrazino, HONH, isocyanato, sulfoxide, sulfone, sulfide, disulfide, silyl, aryl, heterocyclyl, carbocyclyl, intercalator, reporter molecule, conjugate, polyamine, polyamide, polyalkylene glycol, a polyether group, and their derivatives (p. 15-16).

The compounds of McGee et al., particularly those wherein the 2'-O is substituted by R1-(R2)n, wherein R1 = C3-20 alkyl, and R2 is amino, alkyl amino, NH-alkyl, NH-aryl, N-dialkyl, and NH-aralkyl, have clear structural similarity to the broad genus of 2-O-alkylamino and 2'-O-substituted alkylamino compounds of the instant application. The McGee et al. derivatized oligonucleotides have similar properties as Applicants' compounds, namely such modifications enhanced binding affinity to target nucleic acid, nuclease stability and increased pharmaco-dynamic and pharmacokinetic properties of oligonucleotides (see page 7, lines 15-16; examples 90-91). McGee also provides for a process for making the compounds of the claims (e.g., see claims 9-61, 64-65). Additionally, the derivatized oligonucleotides of McGee et al. are

disclosed as being useful for the same purposes as the claimed compounds, including for the formulation of therapeutic compositions and for use in therapeutic methods. McGee specifically teaches that the compound can be formulated as therapeutic compositions that can be used for inhibiting expression for therapeutic treatment (e.g. see pages 23, 63, claims 66-67, etc.).

According to Examples 90-91 of McGee et al., 2'-O-alkyl guanosine residues incorporated into antisense oligonucleotides increases the hybridization specificity of the modified antisense oligonucleotide for its target nucleic acid. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made modify oligonucleotides in the 2'-O position of the ribofuranosyl ring with alkylamino or alkyl-N-substituted groups because these modifications is were taught by McGee to enhance the functional properties of modified oligonucleotides over that of unmodified oligonucleotides. Therefore, the invention as a whole would have been prima facie obvious at the time of filing over, McGee et al.

1. Claims 57 and 58 are rejected under 35 USC 103(a) as being obvious over Monia et al. (US 5,744,362) in view of McGee et al. (WO 94/02501; cited by Applicants).

Monia et al. disclose antisense oligonucleotides having 2'-O-alkyl substituted nucleobases. The 2'-modified oligonucleotides of Monia et al. have been shown to increase both affinity of the oligonucleotide for its target and nuclease resistance of the oligonucleotide (col. 6, lines 25-34). In addition, Monia et al. disclose multiple antisense oligonucleotides targeting mRNA, one particular functional phosphorothioate modified antisense oligonucleotide comprises the identical sequence according to SEQ ID NO: 2 of the instant application. 5'-

T-C-C-C-G-C-C-T-G-T-G-A-C-A-T-G-C-A-T-T-3'. However, Monia et al. does not disclose the modifications described according to formula (I) in claim 1 of the instant application.

As indicated above, McGee et al. teach nucleosides comprising modifications at the 2'-O of the ribofuranosyl ring as described above, wherein said modifications enhance the functional properties of oligonucleotides. These modifications are disclosed as having similar properties as the 2'-modifications disclosed by Monia et al., specifically wherein said modification confers enhanced affinity for target nucleic acid and enhanced nuclease stability

It would have been obvious to one of ordinary skill in the art at the time of filing of the instant application to combine the modifications disclosed by McGee et al. with the modified antisense oligonucleotide taught by Monia et al. One of ordinary skill in the art would have been motivated to combine the teachings of McGee et al. and Monia et al. because they are disclosed as having similar properties and are useful for the same purposes. Furthermore, one of ordinary skill in the art would have had a reasonable expectation that such derivatized oligonucleotides would have enhanced functional properties, i.e. enhanced target site affinity and increased nuclease resistance, based on the teachings of Monia and McGee.

Therefore, the instant claims would have been prima facie obvious at the time of filing over, Monia et al. in view of McGee et al.

2. Claims 1-9, and 11-32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ravikumar et al. (US 5,571,902) in view of Martin (US 5,750,673).

The instant claims read on an oligonucleotide derivative comprising at least one nucleoside building block of formula (I), these building blocks have a 2'-sugar modification of the following basic formula: -O-CH2-A, wherein A is –C(H)(R3)-N-(R1)(R2).

Ravikumar et al. disclose a synthetic process for the solution phase synthesis of phosphorothioate oligonucleotides comprising 2'-sugar modifications and modified internucleotide linkages. The 2'-sugar modifications disclosed as useful in the invention of Ravikumar et al. include SH, SCH_3, F, OCN, -O-$(CH_2)_n$ NH_2, $O(CH_2)_n$ CH CH_3 where n is from 1 to about 10; C_1 to C_{10} lower alkyl, substituted lower alkyl, alkaryl or aralkyl; Cl, Br, CN, CF_3, OCF_3, O-, S-, or N-alkyl; O-, S-, or N-alkenyl; $SOCH_3$, SO_2 CH_3; ONO_2 ; NO_2 ; N_3 ; NH_2 ; heterocycloalkyl; heterocyclo-alkaryl; aminoalkylamino; polyalkylamino; substituted silyl; an RNA cleaving group; a conjugate group (such as polyamines or polyamides (col. 12, line 38-39); a reporter group; an intercalator; a group for improving the pharmacokinetic properties of an oligonucleotide; or a group for improving the pharmacodynamic properties of an oligonucleotide (col. 3, lines 36-52). Groups that enhance the pharmacodynamic properties, in the context of this invention, include groups that improve oligomer uptake, enhance oligomer resistance to degradation, and/or strengthen sequence-specific hybridization with RNA. Groups that enhance the pharmacokinetic properties, in the context of this invention, include groups that improve oligomer uptake, distribution, metabolism or excretion (col. 12, lines 45-54). Moreover, the modified oligonucleotides of this invention also include nucleotides comprising a modified nucleobase, such as 2-aminoadenosine or 5-methylcytosine (col. 14, lines 29-36).

The compounds of Ravikumar et al. and those of the claimed invention are the same except that Applicant's compounds are limited to those oligonucleotides comprising modified nucleoside bases having a 2'-modification of formula (I) of the instant application.

However, it would have been obvious to one having ordinary skill in the art at the time the invention was made to modify the oligonucleotides of Ravikumar et al. such that the 2'-sugar modification is polyalkylamino or more specifically -O-$(CH_2)_n$ NH_2, according to applicant's claimed 2'-O-modifications. It would have been obvious to select the -O-$(CH_2)_n$ NH_2 [which is encompassed by Applicant's formula (1), wherein R1, R2, and R3 are H] modification from the genus of 2'-sugar modifications of Ravikumar et al. because all members of this genus are disclosed as being functionally equivalent in the synthetic process disclosed by this reference. One of ordinary skill in the art seeking alternative modified oligonucleotides would have been motivated to synthesize the modified oligonucleotides as disclosed by Ravikumar et al., specifically wherein the 2'-modification is -O-$(CH_2)_n$ NH_2, since such a modification would produce a compound with similar properties as Applicants compounds, and furthermore Ravikumar et al. does not suggest that this particular substitution would change the properties of the compound in a significant way. Additionally, this reference suggests that this modification would likely enhance the properties of the modified oligonucleotide, particularly by improving oligomer uptake, enhancing oligomer resistance to degradation, and/or strengthen sequence-specific hybridization with RNA, or improve oligomer distribution, metabolism or excretion.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 58 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Claim 58 reads on an oligonucleotide derivative according to claim 57, wherein the oligonucleotide derivative possesses a base sequence according to SEQ ID NO: 2 or a base sequence which is analogous thereto. (Emphasis added).

5. The term "analogous" renders the claim indefinite because the metes and bounds of the term are undefined by the specification and it would not be readily apparent to one of ordinary skill in the art what an oligonucleotide "analogous" to the sequence of SEQ ID NO:2 is, and what it is not. It is noted that changing the phrase "a base sequence which is analogous thereto" to "the RNA sequence encoded by SEQ ID NO: 2" would obviate this rejection.

Claim Objections

6. Claim 58 is objected to because of the following informalities: the phrase "SEQ.ID.NO.2" is not in compliance with standard guidelines for sequence disclosures. It is

noted that changing "SEQ.ID.NO.2" to "SEQ ID NO: 2" would obviate this objection.

Appropriate correction is required.

Response to Arguments

7. Applicant's arguments have been fully considered and are persuasive. Therefore, the rejection(s) previously set froth have been withdrawn. However, upon further search and consideration of the claims, a new ground(s) of rejection is made for the reasons set forth herein.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. E. ANGELL whose telephone number is 571-272-0756. The examiner can normally be reached on Monday-Thursday 7:00 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Fereydoun Sajjadi can be reached on 571-272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. E. ANGELL/
Primary Examiner, Art Unit 1635